SUMMARY MINUTES

MEETING OF THE CIRCULATORY SYSTEM DEVICES ADVISORY PANEL

OPEN SESSION

September 9, 2002

Gaithersburg Holiday Inn
Gaithersburg, MD

Circulatory System Devices Advisory Panel Meeting
September 9, 2002

Attendees

Acting Chairperson
Warren K. Laskey, M.D.
Cardiologist

Executive Secretary
Elisa Harvey, DVM, Ph. D.
Food and Drug Administration

Geretta Wood
Food and Drug Administration

Voting Members
Salim Aziz, M.D.
University of Colorado

Julie A. Freischlag, M.D.
UCLA School of Medicine

Consultants
Kent R. Bailey, Ph.D.
Mayo Clinic

Anthony Comerota, M.D.
Temple University

Kenneth E. Najarian, M.D.
University of Vermont College of Medicine

Michael J. Pentecost, M.D.
Georgetown University Medical Center

Bruce A. Perler, M.D.
Johns Hopkins University

Ileana Piña, M.D.
University Hospitals of Cleveland

Anne C. Roberts, M.D.
UCSD Medical Center/Thornton Hospital

Anton Sidawy, M.D.
VA Medical Center, Washington, DC

Christopher J. White, M.D.
Ochsner Clinic

Consumer Representative
Robert A. Dacey

Industry Representative
Andrew K. Balo
DexCom, Inc.

Food and Drug Administration
Bram Zuckerman, M.D.
Dorothy Abel
Paul L. Chandeysson, M.D.
Doyle Gantt

CALL TO ORDER

Acting Panel Chair Warren K. Laskey, M.D., called the meeting to order at 10:32 a.m. and stated that the purpose of the meeting was to discuss and make recommendations on PMA P020002 for the : P020004, EXCLUDER Bifurcated Endoprosthesis.

Executive Secretary Elisa Harvey, DVM, Ph.D., read the conflict of interest statement. Panel consultant Bruce A. Perler, M.D., had received a waiver for his interests in a firm that could be affected by the outcome of the panel's deliberations and could participate fully in the meeting. The Agency took into consideration other matters concerning panel member Julie Freischlag, M.D., and panel consultants Kenneth E. Najarian, M.D., Michael Pentecost, M.D., and Anne C. Roberts, M.D., all of whom reported interests in firms at issue in matters not related to the day's agenda; the Agency determined that they could participate fully. Due to regulations governing covered relationships, Panel Chair Cynthia Tracy did not participate in the day's deliberations. Dr. Laskey then asked the panel members to introduce themselves.

Elisa Harvey then read the appointment to temporary voting status: Panel consultants Kent R. Bailey, Ph.D., Anthony Comerota, M.D., Kenneth E. Najarian, M.D., Michael J. Pentecost, M.D., Bruce A. Perler, M.D., Ileana Piña, M.D., Anne C. Roberts, M.D., Anton Sidawy, M.D., and Christopher J. White, M.D., had been appointed voting members for the duration of the meeting. In addition, Dr. Warren Laskey had been appointed panel chair for the duration of the meeting. Dr. Harvey noted that Ileana Piña, M.D., a consultant to the Cardiovascular and Renal Drugs Advisory Committee of the Center for Drug Evaluation and Research of FDA had been appointed to the panel as a voting member for the duration of the meeting.

OPEN PUBLIC HEARING

Rodney A. White, M.D., chief, Vascular Surgery, Harbor-UCLA Medical Center, presented information on the Lifeline Registry for Endovascular Grafts. The registry provides longitudinal observational data on abdominal aortal aneurysm (AAA) endograft performance. The goal is to develop comprehensive, long-term outcome data on the safety and effectiveness of endovascular grafts used in aneurysm repair. Key stakeholders include clinicians, medical societies, the Lifeline Foundation, manufacturers, and Federal agencies. Surveillance is a big clinical problem, and the registry represents a collaborative industry effort to be proactive in this area.

In response to panel questions, Dr. White clarified that the database has two parts. Part A is the manufacturers' dataset; compliance is voluntary, but because FDA allows manufacturers to use registry data in their annual reports, they have high incentive to participate. Part B, a clinical tool, is available to individual practitioners through the Web site. The registry is supported by the Society for Vascular Surgery, the American Society for Vascular Surgery, and industry.

SPONSOR PRESENTATION

John Sininger, vice president and general manager, Gore Medical Products Division, described the company, its products, and history. The company has been manufacturing medical products for more than 25 years, and more than 7.5 million implants of Gore Medical products have taken place worldwide. The company has a clear understanding of the need for safe and effective treatment of AAA disease.

David Williams, RN, technical director, Gore Aortic Products, provided an overview of the device. The EXCLUDER Bifurcated Endoprosthesis (EBE) device is bifurcated and modular and has a fully supported, self-expanding, nitinol stent that supports a

polytetrafluoroethylene (PTFE) vascular graft on a blood contact surface. A unique feature is that the outer nitinol exoskeleton is attached to the underlying graft material without sutures. Mr. Williams described how the device is deployed and noted that the results of all preclinical evaluations, including toxicology, biocompatibility, and in vivo studies, demonstrate that the EBE system meets FDA's functional requirements. The device under consideration is the first-generation EBE device. The pivotal trial that is the basis for the PMA data began enrolling patients in December 1998 and stopped in January 2000, although follow up is ongoing. The pivotal study data include events through February 29, 2002. The primary and secondary hypotheses have been evaluated through 12 months, and the protocol allows for patient follow up for 5 years.

David C. Brewster, M.D., clinical professor of surgery, Harvard Medical School, described the epidemiology and natural history of AAA disease. Men over age 65 make up the largest patient cohort; a true increase in prevalence has occurred as a result of the aging of the population. Dr. Brewster noted that the decision to do surgical aneurysm repair lacks scientific precision—it is based on the balancing of risks. Aneurysm size is the most important factor in determining rupture risk. Dr. Brewster said that standard surgical repair is effective and durable, but there is room for improvement: Mortality is 5 to 10 percent in population-based studies. In addition, recovery takes 2 to 3 months, and many patients never recover their preoperative baseline status. High-risk patients are therefore often denied repair. Endovascular repair is similar to standard open surgical grafting but uses only a small groin incision and minimal anesthesia. The EBE device is attached to healthy vascular tissue.

Dr. Brewster then described a classification system for endoleaks. Type I involves proximal or distal attachment, Type II involves retrograde branch flow, Type III is a structural defect or junction, and Type IV is transgraft leakage.

David C. Naftel, Ph.D., professor of surgery, Division of Cardiothoracic Surgery, University of Alabama at Birmingham, described the pivotal trial design and study management along with the study's primary safety and efficacy hypotheses. The study is an ongoing, multicenter, prospective, intent-to-treat design; it includes a nonrandomized, concurrent, open surgical control group. An independent core laboratory reviewed the imaging data. In addition, a clinical events committee and data safety monitoring board reviewed adverse events. Dr. Naftel described the justification for the sample size and stated that a total of 78 control patients and 156 EBE patients had enrolled. He noted the statistical analyses performed and listed inclusion and exclusion criteria. Follow up took place at various intervals and included contrast-enhanced CT, abdominal x-ray, bilateral ankle brachial index, and physical exam. Nineteen U.S. centers participated, including academic, nonacademic, and community hospitals.

Jon S. Matsumura, M.D., assistant professor of surgery, Division of Vascular Surgery, Northwestern University Medical School, presented the study results. The treatment and control groups are statistically comparable. Using the Society for Vascular Surgery risk factor score systems, the EBE group had more hyperlipidemia than the control group. Most aneurysms were 5.0 mm or larger in size.

Regarding the safety hypotheses, the data showed no differences between the EBE and control groups in rates of adverse events after 30 days. Control group participation was a strong independent risk factor for early major adverse events: The proportion of patients free from major adverse events before 30 days was 14 percent in the EBE group, but 57 percent in the

control group. Survival was similar in the EBE and control groups. Participation in the EBE group was not an independent risk factor for mortality.

Regarding the efficacy hypotheses, aneurysm size generally did not change, or it decreased. In 7 percent of EBE patients, aneurysm size increased. Reinterventions were performed on 15 patients, primarily for endoleak. Dr. Matsumura listed the complications and noted that aneurysm rupture did not occur in the study, but two ruptures have occurred in Europe and one occurred in the U.S. feasibility study. The success rate was 80.6 percent. Dr. Matsumura described findings from imaging studies and data related to the secondary hypotheses.

In addition, 24 month follow-up data are available; compliance rates are greater than 90 percent in both groups. A total of 93 percent of control patients and 87 percent of EBE patients are alive, a difference that is not significant. Most patients have no endoleaks; those that do have mostly Type II. Investigators developed a treatment guideline for endoleaks. A total of three late conversions took place, involving one case of aneurysm enlargement with no endoleak and one case of endoleak and aneurysm enlargement. One patient died of endocarditis, but no signs of infection were found at the procedure site. The sponsor concluded that EBE is a safe and effective AAA treatment.

Panel Questions for Sponsor

Panel members asked questions concerning how the ratio of EBE to control patients was achieved, the importance of the proximal aortic neck angle, and postoperative anticoagulant therapy. Sponsor representatives responded that sites were told ahead of time of that the enrollment goal was a 2:1 ratio and took that into consideration in enrolling patients. Once sites had enough control patients, they tended to stop enrolling them, which fostered the difference in

size between the groups as well. Concerning the proximal neck angle, the sponsor's research indicated that the angle was related to late adverse events, perhaps because it is a marker for more advanced disease; the angle itself is not a problem. No protocol for postoperative anticoagulation was specified; it was at the investigator's discretion. All patients were advised to undergo perioperative heparinization.

FDA PRESENTATION

Doyle Gantt, senior biomedical engineer, Division of Cardiovascular Devices, introduced the FDA review team. He noted that FDA had had an opportunity to review the sponsor's presentation in advance; it accurately summarized the data reviewed by the agency.

Mr. Gantt stated that the FDA reviewed the biocompatibility and integrity of the EBE device. As with other stents used in the vascular system, endovascular grafts may be subject to conditions that may result in loss of device integrity. Depending on the location and type of the breach in integrity, an immediate or eventual clinical consequence may result. An important factor in evaluating device integrity is the difficulty in identifying and confirming the presence of structural failures in vivo.

Mr. Gantt noted that two wireform fractures were identified by the core laboratory. The sponsor's investigation found that both reported fractures were identified in the main body of the graft, not in a seal zone or point of attachment to the aorta. FDA review of the failure analysis is complete, and no additional information has been requested from the sponsor. The sponsor recently reported a fracture identified in an explanted device; the fracture was in the bifurcated region of the device.

Mr. Gantt provided information on the clinical study history and listed the notable issues that the sponsor addressed regarding the clinical data. He stated that all FDA requests for additional information have been satisfied.

Panel Questions for Mr. Gantt

Panel members asked for information on the number of adjunctive procedures performed with the EBE device compared with other devices, and **Paul L. Chandeysson, M.D., medical officer, Office of Device Evaluation,** replied that the rate of adjunctive procedures was relatively low for this type of device. Panel members asked for clarification on the number of CT exams performed and the sponsor's statistical analyses, which FDA representatives answered to the panel's satisfaction. Dr. Piña expressed concern that some deaths were listed as pneumonia or sepsis but were actually the result of a cardiac event: Some of the deaths occurred within a month or two of the procedure, so the categorization may be inappropriate.

OPEN PANEL DISCUSSION

Dr. Comerota, panel reviewer, noted that the pivotal trial was not a randomized trial. Complications of surgery were related to the condition of the patient rather than to the procedure. He challenged the assumption that anatomy was not related to risk factors. Dr. Comerota pointed out that the required sample size was calculated on the assumption of certain complication rates, and efficacy was calculated on the basis of the sample size. The control patients appeared to be at increased risk than the EBE patients because the group included more females, suprarenal clamping, and increased angle of the aortic neck. He complimented the investigators on achieving an exceptionally low operative mortality rate, stating that 1 percent 30-day mortality is

very low; however, he emphasized that 0 percent mortality rate at 30 days does not equal 0 percent operative mortality. He pointed out that two patients died after the 30-day window as a direct result of operative complications.

Dr. Comerota noted the lower rate of early adverse events in the EBE group. No open conversions were reported before 24 months, a result he called remarkable. The number of endoleaks was relatively small. Most of the patients who were converted had an intact graft with no endoleak but with clear or serous fluid in sac. It is unclear whether the fluid relates to a property of the device material. During the entire follow-up period, there was a 14 percent death rate in the ENE group but a 7 percent rate in the controls. Most deaths were not directly related to aneurysm. The sponsor reported a 100 percent delivery rate.

Dr. Comerota concluded by saying that the secondary outcomes demonstrate significant benefit in the EBE group compared with controls. It appears that the EBE device meets the requirements of safety, but in efficacy, the study did not meet the statistical requirements for efficacy based on the a priori effectiveness goal of at least 80 percent set by the manufacturer. Compared with other devices, however, the ENE treatment offers safety and effectiveness with good durability.

Dr. Comerota asked the sponsor for additional information on the relationship between aneurysm size and endoleaks. Dr. Matsumura said that most patients in the study did not have aneurysm enlargement; the growth rate is relatively slow. No ruptures occurred in the pivotal study. Panel members discussed management of aneurysm, the timing of surgery in relation to size, and whether the sponsor planned to make recommendations in those areas. Dr. Matsumura noted that intervention is a matter of physician judgment.

Panel members also discussed the sizing of the device and the requirements for femoral artery size. Dr. Matsumura noted that the device has an iliac extender, which can fit as small as a 10 mm diameter. Oversizing is recommended because it can promote device durability. In addition, patient anatomy must accommodate an 18 French delivery profile, including the introducer sheath.

Panel members raised questions concerning physician training for the device, the relation of BMI and platelet count to risk for complications, and technical details of conversion procedures. Dr. Matsumura noted that conversion is technically challenging and requires suprarenal clamping and care not to damage the aorta.

Panel members expressed concern that patients with endoleaks shortly after surgery were not counted in 12-month follow-up data and that patients whose aneurysms actually grew could be counted as having no growth according to the study definition.

Dr. Bailey, panel reviewer, said that the study probably should have been randomized. He expressed concern that the inclusion criteria were confounded with treatment assignment. He also asked about the impact of anatomy on outcomes. Dr. Matsumura said that the sponsor's literature review indicated that anatomy is a predictor in endovascular repair, which is why anatomical inclusion criteria were developed.

Dr. Bailey and other panel members expressed much concern about the number of patients included in the statistical analysis of efficacy. The sponsor clarified its statistical approach in response to the panel's questions, but the panel still felt that more patients should have been included in the analysis. Panel members noted that 12- to 24-month follow up is not long-term follow up. Panel members also were concerned that 40 postoperative CT scans were

not interpreted and were not included in calculating efficacy. They were troubled that the company did not meet its own success criteria.

Gerry Gray, statistician, cardiovascular devices statistics team, FDA, gave a short presentation on FDA's statistical analysis of the sponsor's submission. He noted that patients were assigned to the EBE or control group according to anatomy or clinician judgment; the effects of treatment versus selection cannot be separated. It is unlikely that any one variable could explain away adverse event rate. The increased mortality in the EBE group is not statistically significant, but that could be an artifact of low power. Concerning the success rate, none of the sponsor's analyses result in a CI above 80 percent. The null hypothesis could not be rejected; therefore, the sponsor did not meet the definition of success set forth in the study protocol.

Panel members also asked for additional information on the presence of serous fluid around the implanted device, and why the rates of KUB* images were low, which the sponsor provided to their satisfaction. In response to the panel's concerns over the sudden deaths in the study, Dr. Matsumura noted that the site investigator conducted extensive investigation. Sudden deaths occurred in the control groups and EBE groups equally.

Panel members noted that the patient brochure says that the most common symptom of AAA is pain, but 90 percent of people have no symptoms. They recommended rewriting the section, and the sponsor agreed to do so. In addition, panel members stressed that it was important for patients to understand that they have to be carefully followed after surgery. Dr. Matsumura stated that the sponsor shares the panel's concerns and has constantly emphasized follow up in physician training.

* KUB stands for "kidneys, ureters, bladder" and is a term for a plain frontal supine radiograph of the abdomen.

PANEL QUESTIONS

1. The primary safety endpoint of the clinical study was the rate of major complications as evaluated through 12 months. Additionally, data are presented for individual adverse events, analyses are provided for risk factors associated with adverse events, and causes of death are provided. A summary of the 24-month results is also included. Please comment on whether the results of the clinical study provide reasonable assurance of safety in the intended population.

The panel concurred that the sponsor had met its safety goal.

2. The primary effectiveness endpoint of the clinical study was exclusion of the infrarenal abdominal aortic aneurysm from the blood circulation, defined by absence of aneurysm enlargement and endoleaks, as evaluated through 12 months. Additionally, data regarding potential problems associated with endovascular treatment (e.g., migration, aneurysm enlargement, endoleaks, ruptures, conversion, device integrity) are presented. A summary of the 24-month results is also included. Please comment on whether the results of the clinical study provide reasonable assurance of effectiveness in the intended population.

The panel expressed concern that the primary effectiveness endpoint was not met with sufficient statistical rigor. From a clinical standpoint, however, the results are satisfactory. Some panel members felt that the results of the clinical study provide reasonable assurance of effectiveness in the intended population, but others were not convinced.

3. The Core Laboratory has reported two cases of wire-form fractures, one identified at discharge in a patient enrolled in the pivotal clinical study, and the other at 12 months in a patient enrolled in the ongoing second generation device study. There have been no adverse events associated with either report, and there is not conclusive evidence to verify the presence or absence of the fractures. Both reported fractures were identified in the main body of the graft, not in a seal zone or point of attachment to the aorta. After the panel packs were sent to the Panel, the sponsor reported a wire-form fracture which was recently identified during the sponsor's analysis of a device explanted in Germany. Details concerning the length of implantation, implanting physician identity, and device lot and serial numbers remain unavailable. Based on the sponsor's analysis it appears that the fracture, which was also located in the main body of the graft in the crotch of the bifurcation, did not result in any clinical complications as ends did not appear to be protruding through the device material or the surrounding tissue. Please comment on the significance of these observations.

The panel concurred that the observations may have some clinical significance, but the rate is too small to be certain. The panel expressed concern that so little information is available.

4. One aspect of the pre-market evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify potential adverse events with the use of the device, and explain how the product should be used to maximize clinical benefit and minimize adverse events. If you recommend approval of the device, please address the following questions regarding product labeling.

    a. Does the INDICATION FOR USE, as stated below, adequately define the patient population studied, and for which the device will be marketed?

The EXCLUDER Endoprosthesis is intended to exclude the aneurysm from the blood circulation in patients diagnosed with infrarenal AAA disease who have appropriate anatomy.

The panel concurred that the indication should include more precise dimensional data on the appropriate iliac vessel size and aneurysm size of patients receiving the device.

b. Based on the clinical investigation experience, are there any additional warnings, precautions, or contraindications that you think should be included, either specific to this device or from a generic standpoint for endovascular grafts?

The panel felt that warnings should be included on the following issues: fractures, early endoleaks, the safety of intervention in cases of bilateral iliac artery occlusion, the lack of long-term follow up on the device, the need for annual CT and KUB scans (or MRIs), and the risk of device migration.

c. Please comment on whether the instructions for use adequately describe how the device is to be delivered.

The panel concurred that the instructions were adequate.

d. Do you have any other comments on the labeling?

The panel had no further comments.

5. Please comment on the adequacy of the proposed physician training plan, as described in the panel package.

The panel concurred that the proposed training plan was adequate, although one panel member expressed concern that inexperienced physicians could have access to the device.

6. The sponsor is proposing to conduct a post-approval study on the patients enrolled in the pivotal clinical study (i.e., 235 test patients and 99 controls). Five-year follow-up on all patients who are alive and not withdrawn from the study will be obtained in accordance with the clinical protocol approved under the IDE for this device. Please comment on the acceptability of this plan, as briefly described in the panel package.

The panel noted the difficulty of locating patients once they have withdrawn from a study because contacting them violates IRB protocols. The panel recommended that the sponsors conduct 5-year follow up of all study patients to the extent possible.

Consumer Representative Robert Dacey stated that the patient brochure was well done. He encouraged FDA and the sponsors to look at what works and what does not work in patient education. Research is finding that when asking people to change their behavior, the only thing that works is tutoring.

Industry Representative Andrew Balo stated that the device is equivalent to procedures that are currently used. Less invasive procedures are better for patients. Other sponsor data show that the device is beneficial.

PUBLIC COMMENTS

Takao Ohki, M.D., chief, vascular and endovascular surgery, Montefiore Medical Center, stated that he has hands-on experience with the device through participating in the clinical study. He noted that because the EBE device has unique advantages over other devices, many patients traveled to his site from elsewhere. He expressed his hope that the panel would not reject the device because of the statistical issues.

Mark Fillinger [sp?], vascular surgeon, Dartmouth-Hitchcock Medical Center, said that he has used this and many other approved devices. His experience with the sponsor has been very good, and he believes that no attempt has been made to misconstrue data in any way.

Roy K. Greenberg, M.D., director, endovascular research, Cleveland Clinic, said that he does not believe that the EBE device is different from any of the two commercially available

devices. A fracture rate of 3 percent is low when not associated with clinical manifestations. The real problem was that the study design used an 80 percent success rate.

Dr. White noted that if a core laboratory's can evaluate 70 or 80 percent of the images, that is a good rate. The x-rays that are taken at the clinical level need greater consideration. In his opinion, 95 percent or more of the patients had treatment on the basis of what the clinician saw at time of treatment.

Dorothy Abel, biomedical engineer, Office of Device Evaluation, pointed out that over time, researchers and FDA learn that they may have focused on less than optimal surrogate endpoints. Studies cannot be designed to look at aneurysm rupture, and endoleak itself does not appear to be a good surrogate endpoint. FDA is still struggling with the best way to evaluate these devices.

Dr. Matsumura pointed out that the sites obtained CTs on 93 to 97 percent of the patients; they are not evaluable for endoleak, but they are good for obtaining other information.

PANEL RECOMMENDATIONS AND VOTE

Executive Secretary Harvey read the voting options. A motion was made and seconded to approve the device with the following conditions:

1. Mandatory 5-year follow up should be conducted on all patients in the pivotal study cohort.
2. The sponsor should obtain information on the 40 outstanding CTs and submit it to FDA and the panel.
3. The instructions for use should stress sources of comorbidities and mortality, and the patient labeling should include that information as well.

The motion passed by a vote of 10-1. In addition, the panel recommended by a vote of 10-1 that the patient brochure indicate that follow up for imaging and therapy is vital.

In explaining the reasons for their votes, panel members stated that the sponsor had demonstrated safety and effectiveness of the device. They noted that their concerns about missing data and follow up were satisfied by the conditions of approval. Several panel members noted the ease of deployment of the device and the high rate of insertion success. The panel member who voted against the device stated that the device is clearly a good one, but the data did not demonstrate effectiveness.

ADJOURNMENT

Dr. Laskey thanked the participants and adjourned the meeting at 6:23 p.m.

I certify that I attended this meeting of the Circulatory System Devices Advisory Panel Meeting on September 9, 2002, and that these minutes accurately reflect what transpired.

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Elisa Harvey, DVM, Ph.D.
Executive Secretary

I approve the minutes of this meeting
As recorded in this summary.

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Warren K. Laskey, M.D.
Acting Chairperson

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